

Perineural Invasion by Transitional Cell Carcinoma of the Bladder in Patients submitted to Radical Cystectomy: What is the Prognostic Value?

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ABSTRACT

Objective: Determine the prognostic value of perineural invasion (PNI) in patients with transitional cell carcinoma (TCC) of the bladder treated with radical cystectomy.

Materials and Methods: From January 1993 to January 2005, 113 people were selected from 153 patients with TCC of the bladder treated with radical cystectomy. The association between the presence of PNI and other pathologic characteristics were analyzed through Fisher exact test. The Kaplan-Meier method was utilized to assess the survival curve and the statistical significance was determined by the Breslow test. The multivariate analysis was performed through the Cox regression model.

Results: The PNI was identified in 10 (8.8%) of the 113 patients. This variable significantly related to the microvascular invasion and to tumor staging. The mean segment after surgery was 31.7 ± 28.5 months. Recurrence occurred in 5 (50%) and in 41 (39.8%) patients ($p = 0.363$) and mortality occurred in 2 (20%) and 22 (21.9%) patients ($p = 0.606$) with or without PNI respectively. In Cox regression analysis, patients with PNI presented with 1.53 times (IC 95% 0.60 to 3.91; $p = 0.371$) and 1.60 times (IC 95% 0.37 to 6.95; $p = 0.532$) the risk of recurrence and mortality when compared to patients without PNI.

Conclusions: The PNI does not constitute an independent variable of disease-free and cancer specific survival in patients with TCC of the bladder treated with radical cystectomy.

Key words: bladder neoplasms; carcinoma; transitional cell; cystectomy; prognosis

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INTRODUCTION

Radical cystectomy continues being the main form of treatment for patients with muscle-infiltrating bladder tumors (1,2). However, despite this aggressive approach, in approximately 5 years, 50% of the patients will die due to the disease (3). For this reason, a new prognostic factor capable of determining the

biologic behavior of such tumors is necessary to better select patients that are candidate to adjuvant therapy.

Perineural invasion (PNI) is an uncommon form of tumor dissemination that is related to an unfavorable prognostic in patients with head and neck, gullet and pancreas tumors and colorectal carcinoma (4-8). In prostate cancer, some studies have demonstrated that the presence of PNI in the biopsy

specimens is related to the finding of extra-prostatic extension in the surgical specimen, which is an important data at the moment of the determination of the patient's prognostic (9,10).

On the other hand, in patients with muscle-infiltrating bladder cancer while the value of the tumor stage, grade, presence of carcinoma in situ and lymph node (LN) involvement are being widely studied, our knowledge as to the frequency and significance of the PNI is minimum. The PNI is reported in 6.8 to 47.7% of the patients with transitional cell carcinoma (TCC) of the bladder treated with radical cystectomy (1,2,11-14). While in the majority of such studies the PNI is related to disease-free survival (12,14) and global survival (2,12) only in univariate analysis, others have demonstrated that the PNI also presents a prognostic value in multivariate analysis (13).

The aim of the present study is to analyze the relation of PNI with other pathological characteristics and its prognostic value in the determination of the disease-free and cancer specific survival in patients with TCC of the bladder treated with radical cystectomy.

MATERIALS AND METHODS

During the period from January 1993 to January 2005, 153 patients were selected with muscle-infiltrating TCC of the bladder that were treated with radical cystectomy, bilateral iliac lymphadenectomy and an orthotopic ileal neobladder. From those, 8 were treated with neoadjuvant chemotherapy, 18 had incomplete information, 8 had other histological types and 6 did not have any available segment being excluded from the study. The 113 other patients were the base for this study.

The preoperative diagnosis was performed through transurethral resection. All patients were staged with thoracic radiography and computerized tomography of the abdomen and pelvis and were considered as having a localized disease. CR indications included the presence of tumors compromising the muscular layer (T2), and superficial tumors refractory to intravesical or multifocal therapy. Fifteen patients with extravesical disease were

submitted to adjuvant chemotherapy with methotrexate, vinblastine, adriamycin and cisplatin (M-VAC).

Risk factors analyzed were age, gender, pathological stage, tumor grade, tumor size, the presence of CIS, the presence of PNI, microvascular invasion (MVI) and LN involvement. The analysis of the pathological stage and tumor grade was performed through the 1997 TNM and the 2004 WHO (World Health Organization) systems respectively (15,16). For the pathological stage we have used T0, Tis, T1, T2 (T2a + T2b), T3 (T3a + T3b) and T4 categories. Grade 1 and 2 tumors were considered low grade and 3 and 4 high grade. The PNI was defined as either the presence of tumor infiltration in the perineural sheath or in the endoneurium (Figure-1).

In the postoperative period, the segment consisted in a visit 2 months after the surgery and every four months until completing 1 year. After this period patients were seen every 6 months or before in case of progression or death. In each visit, patients were submitted to a clinical exam, thoracic radiography and computerized tomography of the abdomen and pelvis.

The main variables studied were disease-free and cancer specific survival rates. Patients that died due to other causes were considered as censors and followed until the date of the death. Correlations between the presence of PNI and other pathological

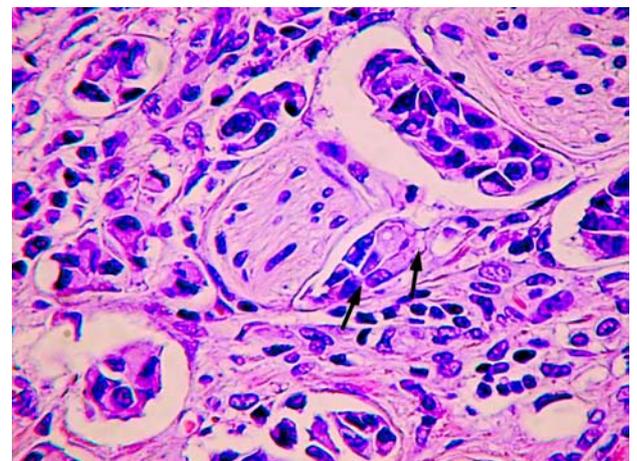


Figure 1 – Perineural invasion by the transitional cell carcinoma of the bladder (arrows).

characteristics were analyzed through the Fisher exact test. The Kaplan-Meier method was utilized to determine the curve of survival and the statistic significance assessed through the Breslow test. The multivariate analysis was performed through the Cox regression model with a confidence interval (CI) of 95%. The value of $p < 0.05$ was considered statistically significant. Statistics calculations were performed in the software SPSS 12.0 for Windows.

RESULTS

Mean patient's age was of 65.9 years (42 to 90 years) and 85.8% were male. MVI was observed in 48 (42.5%) of the 113 patients. Forty-six (49%) patients presented with tumors of less than 3 cm and 47 (51%) tumors measuring 3 cm or more. Many patients were submitted to more than one transurethral resection before the cystectomy and in 29 cases the tumor size could not be measured. Thirty nine percent presented extravesical disease (T3 or T4), and 86.9% of the patients presented high-grade lesions. The presence of concomitant flat CIS (carcinoma in situ) and the involvement of LN were observed in 40.7%

and 15.7% of the cases respectively. Twenty-nine and 43 patients did not have information regarding the tumor grade and the state of the LN respectively.

PNI was present in 10 (8.8% - CI 95% = 4.3% to 15.7%) patients. The presence of PNI associated significantly to the tumor stage and to the presence of MVI (Table-1). Ninety percent of the patients with PNI presented with MVI and only 37.8% of the patients without PNI presented it ($p = 0.002$). While no patients with stage T0 or T1 presented with PNI, 50% and 40% of the patients with stage T3 and T4 respectively presented it ($p < 0.001$). The age, gender, grade and size, the presence of CIS and the state of the LN did not present any relation to the PNI ($p > 0.05$).

Mean follow-up after cystectomy was of 31.7 ± 28.5 months (median of 24 months; 1 to 138). At the end of the follow-up, 46 (40.7%) tumors recurred and 24 (21.2%) patients died due to cancer. No difference was observed in the disease-free neither in the cancer specific survival rates among patients with or without PNI. Recurrence occurred in 5 (50.0%) and in 41 (39.8%) patients (Breslow test; $p = 0.363$), and mortality occurred in 2 (20.0%) and in 22 (21.9%) patients (Breslow test; $p = 606$) with and without PNI respectively (Figures-2 e 3). According

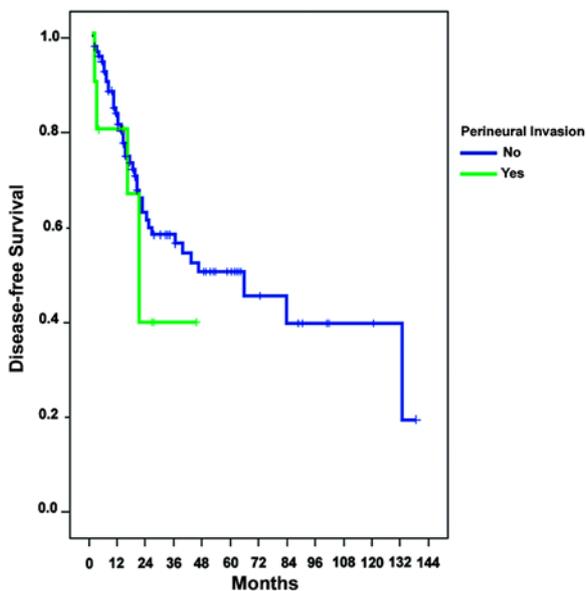


Figure 2 – Disease-free survival of patients with and without perineural invasion.

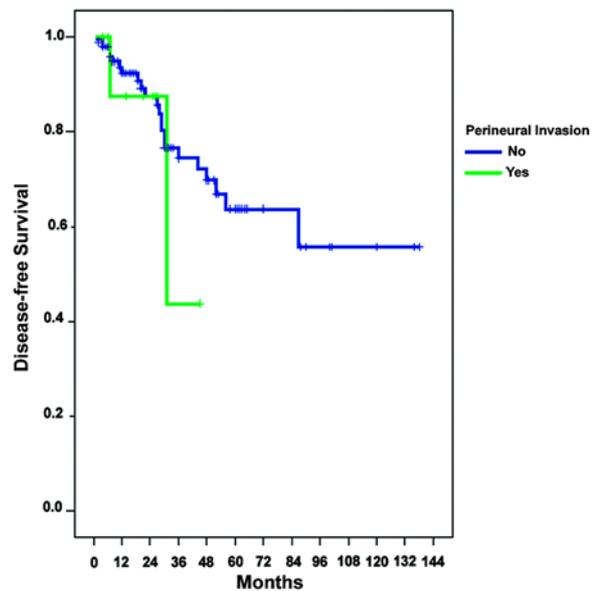


Figure 3 – Cancer-specific survival of patients with and without perineural invasion.

Perineural Invasion by Transitional Cell Carcinoma of the Bladder

Table 1 – Patients’ characteristics according to perineural invasion.

	Perineural Invasion		p Value
	No	Yes	
Age			0.095 ⁺
< 67 years old	53 (51.5%)	2 (20.0%)	
≥ 67 years old	50 (48.5%)	8 (80.0%)	
Gender			> 0.999 ⁺
Female	15 (14.6%)	1 (10.0%)	
Male	88 (85.4%)	9 (90.0%)	
Tumor size			0.267 ⁺
< 3.0 cm	44 (51.8%)	2 (25.0%)	
≥ 3.0 cm	41 (48.2%)	6 (75.0%)	
CA in situ			0.524 ⁺
No	60 (58.3%)	7 (70.0%)	
Yes	43 (41.7%)	3 (30.0%)	
MVI			0.002 ⁺
No	64 (62.1%)	1 (10.0%)	
Yes	39 (37.8%)	9 (90.0%)	
Lymph nodes			> 0.999 ⁺
No	55 (83.3%)	4 (100.0%)	
Yes	11 (16.7%)	-	
Grade			0.229 ⁺⁺
Low	11 (14.9%)	-	
High	63 (85.1%)	10 (100.0%)	
Stage			< 0.001 ⁺⁺
T0	13 (12.6%)	-	
Tis	9 (8.7%)	-	
T1	18 (17.4%)	-	
T2	28 (27.2%)	1 (10.0%)	
T3	30 (29.1%)	5 (50.0%)	
T4	5 (4.9%)	4 (40.0%)	

⁺ Fisher exact test; ⁺⁺ generalization of the Fisher exact test; MVI = microvascular invasion.

to the Cox regression model the PNI did not constitute a variable determinant of recurrence (Hazards Ratio 1.53; 95% CI 0.60 - 3.91; p = 0.371) and mortality (Hazard Ratio 1.60; 95% CI 0.37 - 6.95; p = 0.532) in both uni- and multivariate analysis.

COMMENTS

In the present study, we retrospectively analyzed the prognostic value of the PNI in patients

with TCC of the bladder treated with radical cystectomy. Despite the fact that the presence of PNI significantly relates to the presence of MVI and that the tumor stage was advanced, the disease-free and cancer specific survival rates were not statistically different among patients with and without PNI. In the Cox regression analysis, PNI did not influence the prognostic of the patients in both uni- and multivariate analysis.

PNI has been associated to an unfavorable diagnosis in patients with head and neck tumors (4),

has presented a stage-independent prognostic value and has helped forecast the answer to adjuvant therapy in many patients with gullet, stomach and colorectal carcinoma (5,6,8), and has also been responsible for high recurrence rates in patients with pancreatic tumors submitted to healing resections (7). Among patients with prostate cancer, prognostic value of PNI has been widely studied. Many works have demonstrated that the PNI is capable of previewing the extraprostatic extension and even the response to surgical and radiotherapy treatment (9,10). Cases of prostate cancer with PNI at the biopsy generally present a high Gleason Score, multiple fragments involved and high PSA values. Besides that, these cases have been considered as indications of resection of the neurovascular bundle of the committed side. The resection of the neurovascular bundle of this side can reduce the risk of committed margins in 17.5% (12).

Regarding the patients with TCC of the bladder, our knowledge regarding the frequency and the prognostic value of the PNI is minimum. Some authors suggest that the PNI finding in the specimen of the radical cystectomy is associated to a larger incidence of positive LN and distant metastasis, as well as lower disease-free and cancer specific survival rates when compared to patients without PNI. However, these results were not analyzed through the multivariate regression models and the impact in the prognosis might not have been independent from other significant variables such as tumor grade and stage (12).

Few works analyzing the PNI prognostic value have used multivariate regression models. Bassi et al. (1), analyzing global survival in 369 patients with bladder cancer treated with radical cystectomy as a monotherapy, demonstrated that the PNI was a relevant variable only in univariate analysis. Survival rates in 5 years were 44% and 56% for patients with and without the PNI respectively. In the same way, Leissner et al. (14), have determined that the disease-free survival in 5 years among 283 patients with bladder tumors with and without PNI was of 30% and 60% respectively. However, only the involvement, tumor stage and presence and the MVI had become independent prognostic variables. The PNI prognostic value was also analyzed by Hong et al. (2). A revision

of 125 patients with PNI in 8.8% of the cases found significant differences in global survival rates among patients with and without PNI. However, after control by other variables, the PNI did not demonstrate any impact in prognosis. On the other hand, Knap et al. (13), analyzing 248 patients with a PNI rate of 6.8%, defined that this variable, together with LN involvement and with the presence of MVI, became an independent prognostic factor of cancer specific survival.

In the present study, the PNI was not a determinant prognostic variable of disease-free and cancer-specific survival rates. However, these findings should be cautiously analyzed. A form of explaining this lack of statistic significance is the small number of patients with this finding when compared to other series (1,11,14). This could be well illustrated by the survival curves that have shown a trend to an unfavorable evolution among patients with PNI. At the same time, tumor stage and MVI, that are two of the most important prognostic variables in these patients, are significantly related to the PNI. While no patient with T0 or T1 stage presented PNI, this finding was present in approximately half of the patients with T3 or T4 stage. Besides, approximately 90% of the patients with PNI have also presented MVI. These findings suggest that these patients can really present more aggressive tumors, even though this was not translated in an unfavorable evolution.

Finally, this preliminary study demonstrated that despite a significant relation with MVI and tumor stage, the PNI did not have any impact in the disease-free and cancer-specific survival rates in patients with TCC of the bladder treated with radical cystectomy.

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CONFLICT OF INTEREST

None declared.

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